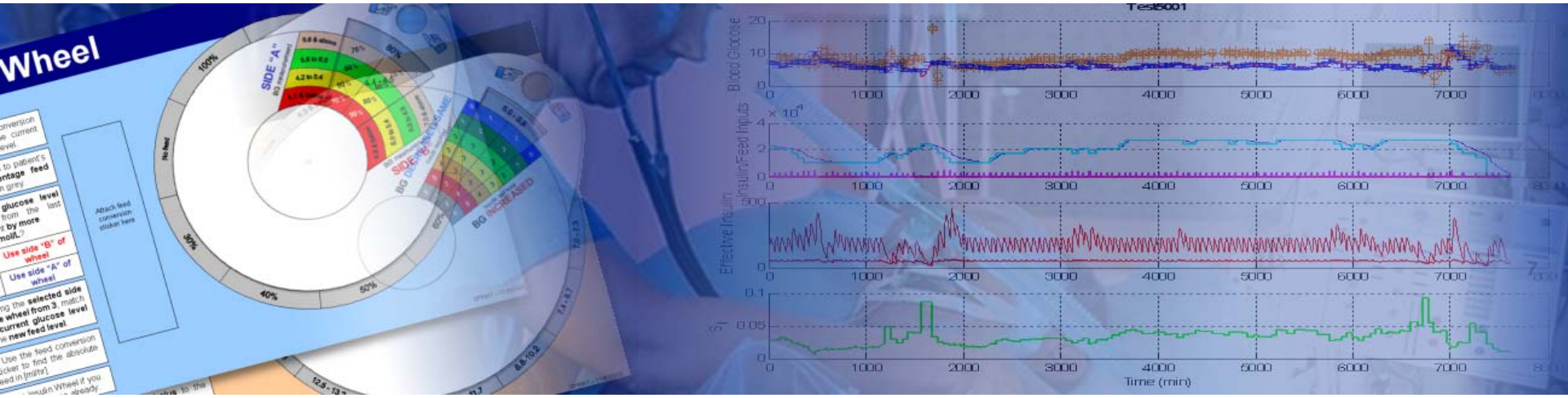
High(er) Insulin Sensitivity Rules Out Sepsis in Critical Care

Advanced sepsis detection as part of tight glucose control



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Med101 For Engineers: Sepsis is bad!

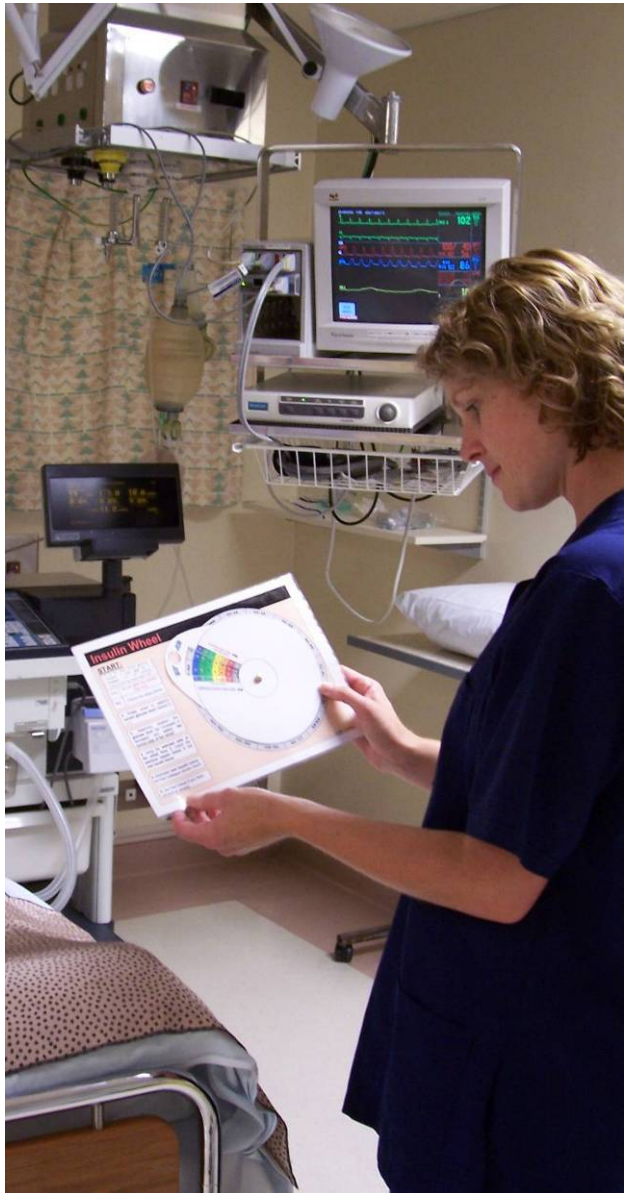
- Sepsis and septic shock in critical care:
  - Significant incidence rates (2-11% for severe sepsis and higher for all forms)
  - Mortality of 30-80% reported
  - Tight glucose control can reduce mortality in sepsis
  - Annual (est.) cost of $16.7 per year in U.S. **[Angus et al, 2001, Crit Care Med]**

- Diagnosis is challenging and early treatment is beneficial
  - **Gold Standard** = positive blood culture should precede treatment but takes 24-48 hours
  - Early goal directed therapy reduced mortality from 46-31% **[Rivers et al, NEJM 2001]**
  - Therefore other markers are often used:
    - Primarily inflammatory and acute immune response markers with 2-3 hour lag on diagnosis and/or results (TNFα, IL-6, IL-8, CRP and PCT) **[Carrigan et al, Clin Chem 2004]**

- **Insulin sensitivity** is significantly affected by sepsis – could it be a marker?
  - Low values indicating sepsis or high values indicating its lack of presence
  - Mechanisms not fully known but assumed related to counter-regulatory and stress response in illness, as well as pro-inflammatory immune response and drug therapy.

- **Hypothesis**: Could an Insulin Sensitivity marker provide a more accurate diagnostic and reduce the preventative use of (broad coverage) antibiotics?

Methods



- Retrospective Study:
  - **143** patients under tight glucose control using SPRINT at Christchurch Hospital
  - **113** w/o sepsis; **30** diagnosed with sepsis
  - Cohort comprises 26,000+ hours of data
- Each hour was given a:
  - Sepsis score (*ss*) on a scale of 0 → 4
  - Clinically validated model-based insulin sensitivity value (S_I)
  - Simplified insulin sensitivity during periods of constant glucose level based on nutrition and insulin inputs (SS_I)
- Patients with T1DM or T2DM were excluded
- Ethics approval from South Island Regional Ethics Committee (New Zealand).

Sepsis Score (ss)

- Strictly clinical metric
- Follows ACCP and SCCM guideline definitions of 1992 and 2003 for sepsis diagnosis
- Includes both SIRS and SOFA scores to account for more than a single criteria
- Inotrope dosing included due to its common use in treating severe sepsis

Sepsis Score

1 Infection & Inflammatory Response (SIRS ≥ 2)

+

2 ≥ 1 Organ Failure & Fluid resuscitation

+

3 Inotrope drugs (low dose)

+

4 Inotrope drugs (high dose)

Sepsis score		Definition					
		SIRS ≥2	Infection during stay	Organ failure ≥1	Fluid resuscitation	Inotrope present	High inotrope dose[a]
0	Normal						
1	Sepsis	✓	✓				
2	Severe sepsis	✓	✓	✓	✓		
3	Septic shock	✓	✓	✓	✓	✓	
4	Refractory septic shock	✓	✓	✓	✓	✓	✓

[a]Adrenaline or noradrenaline ≥0.2 mg min^{-1} kg^{-1}.

Insulin Sensitivity Metrics

- **Model based insulin sensitivity (S_I):**
  - Derived from fitting a dynamic model to the data
  - Model clinically validated in several glycaemic control studies and trials in critical care and *vs.* euglycaemic clamp
  - Readily calculated in real-time by computer

$$\dot{I} = -\frac{nI}{1+\alpha_I I} + \frac{u_{ex}}{V} \qquad \dot{Q} = kI - kQ \qquad \dot{G}_t = -p_G G_t - S_I G_t \frac{Q}{1+\alpha_G Q} + \frac{P(t)}{V_G} + P_{end}$$

- **Simplified insulin sensitivity metric (SS_I):**
  - Matches the ISI of euglycaemic clamp (ISI/G normalisation)
  - Valid during periods of relatively constant glucose levels
  - Can be calculated by hand in real-time

$$SS_I = P(t)\frac{60}{I(t)G_t}$$

Patients

- Retrospective data study
- T1DM and T2DM excluded if diagnosed
- Sepsis patients were all diagnosed by blood culture

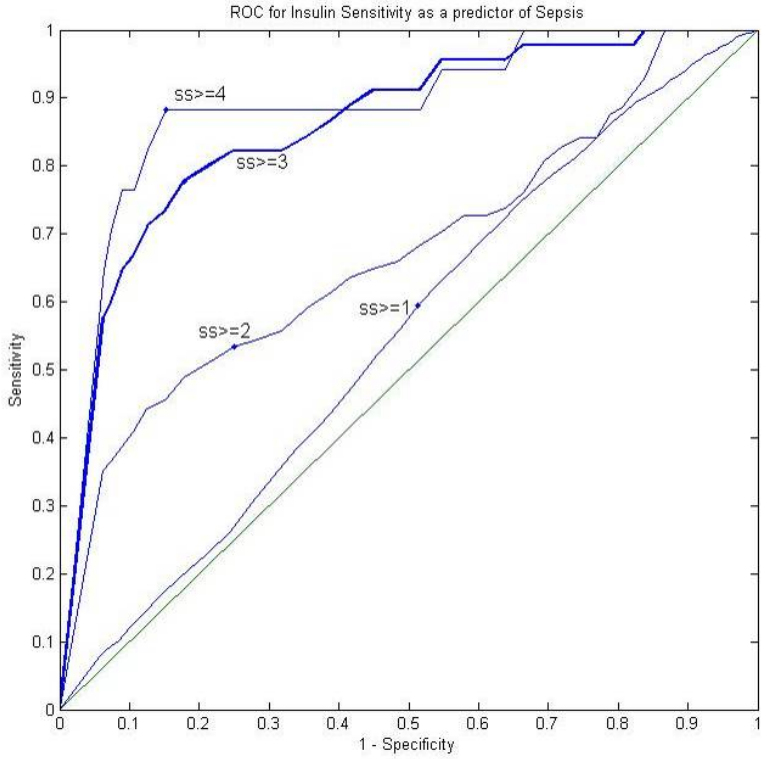
Summary of Patient hours in each subset of the ICU cohort

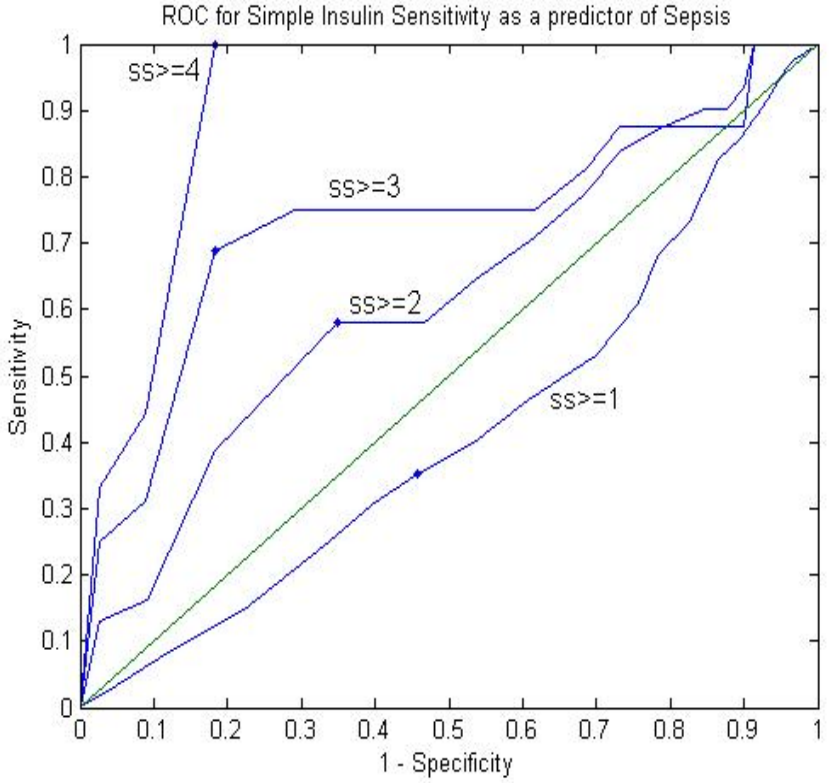
	Sepsis	Non-Sepsis	Total
Number of Patients	30	113	143
Total Hours	6,744	19,709	26,453
Total Hours where dG/dt ~ 0 for SS_I	2,036	5,493	7,529

ROC Results (for $ss \geq 3$)

- **Model based (S_I):**
  - Sensitivity = 78%
  - Specificity = 82%
  - Positive Prediction = 2.8%
  - Negative Prediction = 99.8%
  - S_I Cutoff = 8.5e-5
  - % Measurements < cutoff = 15%

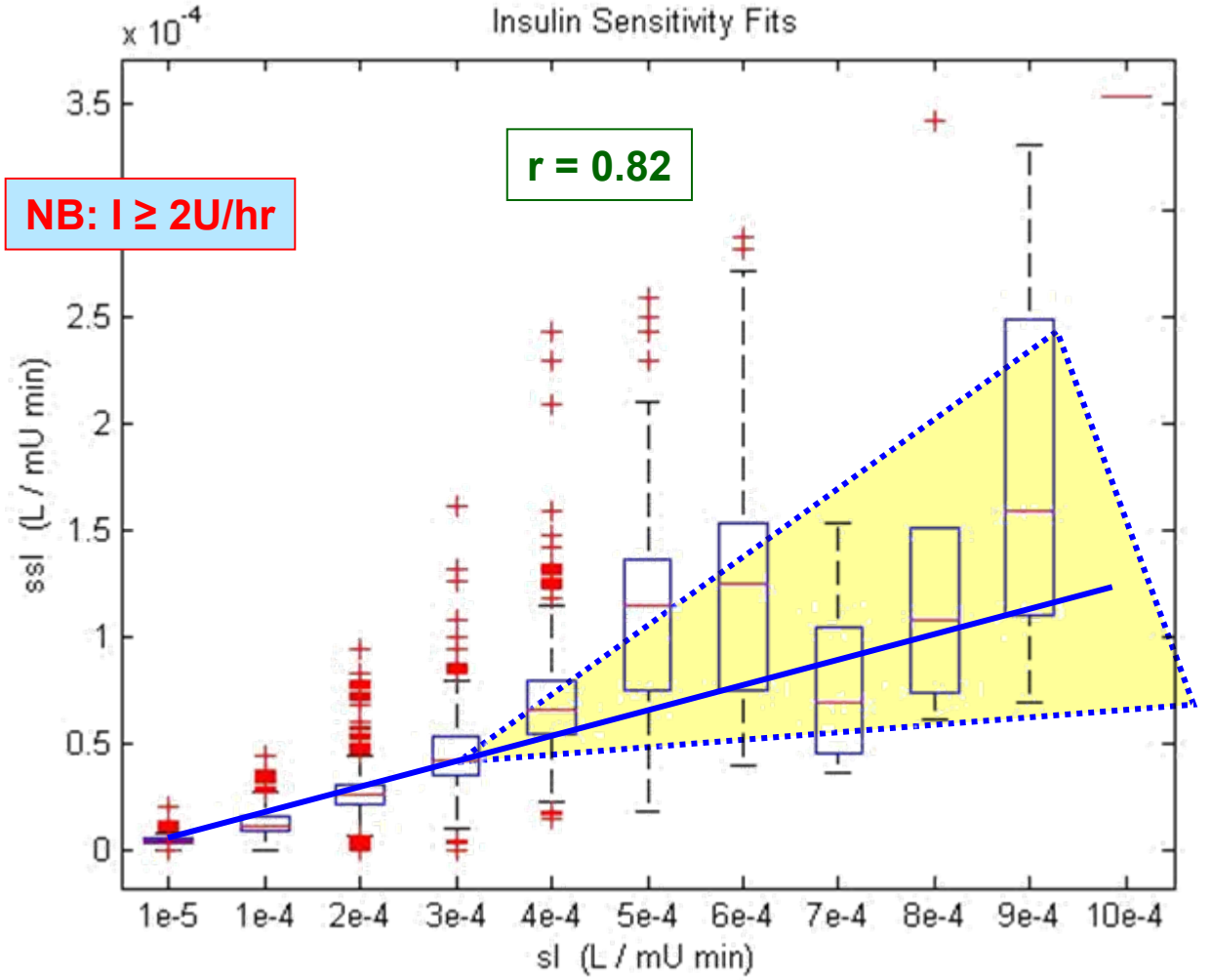
- **Simple (SS_I):**
  - Sensitivity = 69%
  - Specificity = 82%
  - Positive Prediction = 2.5%
  - Negative Prediction = 99.7%
  - Lower numbers of hours





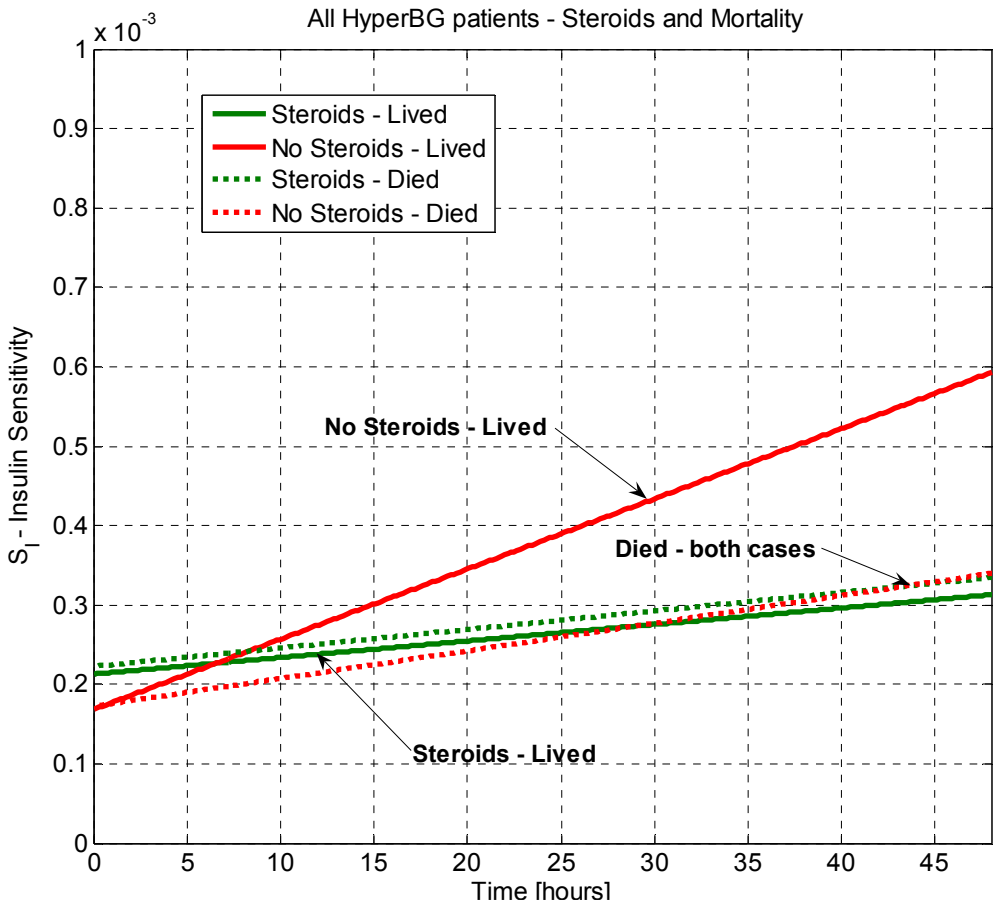
Is SS_I an effective metric?

- Good correlation at low cutoff values
- Spread at higher values above cutoff values
- Spread thus does not affect usefulness of simple metric (SS_I) as a negative predictor of sepsis in place of the model based metric (S_I)



Why not positive prediction?

- Any number of clinical causes of low insulin sensitivity
- Drug therapies can lower insulin sensitivity in survivors
- Mortality and lower insulin sensitivity may also go together (level of acuity)
- These results are from a study of steroids and insulin sensitivity in 53 Subarachnoid Haemorrhage patients
- **Positive prediction will require a way to filter out other causes of low insulin sensitivity**



Conclusions and Positive Prediction

- Both metrics provide **negative prediction** for/over a significant amount of the patient hours.
  - May thus reduce unnecessary preventative antibiotic use

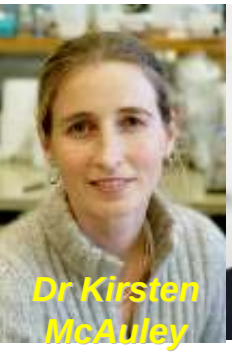
- Both insulin sensitivity metrics can be readily available at bedside
  - S_I requires a model and computation (e.g. PDA)
  - SS_I requires a consistent and an effective glycaemic control protocol

- **Positive prediction** is ~0 because very low insulin sensitivity may be indicative of sepsis or a variety of other conditions and/or drug therapies

- Future necessities:
  - Improve cutoff values and validate prospectively (tighter metric)
  - Better sepsis score?
  - Improve positive prediction via additional heuristics or symptoms in addition to insulin sensitivity to discriminate between sepsis and other conditions?

Acknowledgements … or how I did this all myself!

Dunedin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Don't let this happen to you!


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Jason Wong et al


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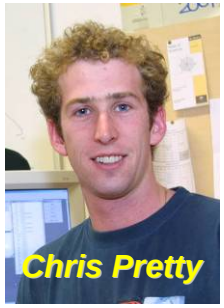
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Questions?